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RESEARCH

Probiotics, Live Biotherapeutic Products (LBPs), and Gut-Brain Axis Related Psychological Conditions: Implications for Research and Dietetics

Duygu Ağagündüz[1] · Elif Çelik[1] · Özge Cemali[1] · Feray Gençer Bingöl[2] · Çiler Özenir[3] · Fatih Özoğul[4,5] · Raffaele Capasso[6]

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Abstract
It is well-known that probiotics have key roles in the crosstalk between the gut and brain in terms of nutrition and health. However, when investigating their role in nutrition and health, it can be important to discriminate probiotics used as foods, food supplements, or drugs. For clarification of this terminology, the Food and Drug Administration (FDA) has established a new "live biotherapeutic products" (LBP) category, expressing pharmaceutical expectations and to reduce confusion in the literature. Growing evidence advises that the community of microorganisms found in the gut microbiota is associated with psychological conditions. Hence, it is thought that LBPs may positively affect depression, anxiety, bipolar disorder, and schizophrenia by reducing inflammation, improving gut microbiota, and balancing gut neurometabolites. This review focuses on the specific position of probiotics as LBPs in psychological conditions. Condition-specific potential pathways and mechanisms of LBPs and the prominent strains are discussed in the light of novel studies for future research, dietetic and pharmaceutical applications.

Keywords Live biotherapeutic products (LBPs) · Gut-brain axis · Probiotics · Psychological conditions

Introduction

The microbiota is a collection of various bacteria, archaea, fungi, protozoa, and even viruses and is the subject of research on the regulation of health and the relationship between diseases [1, 2]. The microbiota is crucial for sustaining normal gut physiology and health. The gut microbiota has many important functions, such as protection from pathogens, supporting the immune system, maintaining digestion and metabolism, influencing the proliferation of epithelial cells, regulating insulin metabolism, and affecting gut-brain cross-talk. In light of all these abovementioned functions, especially gut microbiota can affect mental and neurological functions and health [2].

One of the diseases thought to be linked with alteration in the gut microbiota is psychological diseases. There is

✉ Duygu Ağagündüz
duyguturkozu@gazi.edu.tr

Elif Çelik
elifcelik145@gmail.com

Özge Cemali
dytozgecemali@gmail.com

Feray Gençer Bingöl
gencerferay@gmail.com

Çiler Özenir
cileraslanalp@gmail.com

Fatih Özoğul
fozogul@cu.edu.tr

Raffaele Capasso
rafcapas@unina.it

[1] Department of Nutrition and Dietetics, Gazi University, Emek, Ankara 06490, Turkey

[2] Department of Nutrition and Dietetics, Burdur Mehmet Akif Ersoy University, İstiklal Yerleşkesi, Burdur 15030, Turkey

[3] Department of Nutrition and Dietetics, Kırıkkale University, Merkez, Kırıkkale 71100, Turkey

[4] Department of Seafood Processing Technology, Faculty of Fisheries, Cukurova University, Balcali, Adana 01330, Turkey

[5] Biotechnology Research and Application Center, Cukurova University, Adana 01330, Turkey

[6] Department of Agricultural Sciences, University of Naples Federico II, 80055 Portici, NA, Italy

a relationship between the gut microbiota and the hypothalamic–pituitary–adrenal (HPA) axis. Dysbiosis and increased intestinal permeability may contribute to the release of pro-inflammatory cytokines, microbial antigens, and ileal corticosterone, and some bacteria can produce molecules that increase ACTH synthesis. These affect the HPA axis. At the same time, HPA axis activation can affect microbiota and permeability. Various stressors might impact the abundance of some bacteria and intestinal integrity [3]. Some factors, such as dysregulation of HPA axis, chronic inflammation, immune dysregulation, and gut-brain disorders, have been associated with psychological problems. These factors can affect neuroplasticity, neurogenesis, and neuroinflammation [3, 4]. Changes in the HPA axis may affect brain-derived neurotrophic factor (BDNF) expression, suppress serotonin (5-HT) synthesis, and decrease glutamate (Glu) receptor expression, neuroplasticity, and problems in neuronal circuitry [4]. In general, the microbiota-gut-brain axis has been associated with psychiatric diseases in plenty of pathways, including the vagus nerve, enteric nervous system, immune system, tryptophan metabolism, neurotransmitters, nerve cells, and synaptic properties, and microbial metabolites [5]. For these reasons, many approaches have been developed to regulate the microbiota. Modulation of the gut microbiota and HPA axis using probiotics and their role in the treatment of psychiatric disorders are among the most popular topics nowadays [6].

According to the FAO/WHO, probiotics are live microorganisms which when administered in suitable proportions confer a health benefit on the host [7]. Probiotic features of many bacteria and fungi are observed, but the most widely used probiotics belong to *Lactobacillus* and *Bifidobacterium* species [8]. In general, the definition of probiotics can be used to refer to both a conventional food or food supplement and a drug. However, to the general public, the term probiotic refers mostly to a food or dietary supplement, and much less frequently to a drug or medicinal product. As a result, specific authorities proposed a separate name for pharmaceutical products containing live microorganisms as ingredients [9]. The Food and Drug Administration (FDA) defined live biotherapeutic products (LBPs) as biological products contains live organisms, applicable to the prevention, treatment, or cure of a human disease or condition, and are not vaccines [10]. In Europe, LBPs were formally recognized as a category of medical products in 2019 [11].

Recently, there has been increasing evidence that LBPs are linked to gut-brain axis-related psychiatric conditions by modulating the HPA axis [12, 13]. Herein, promising roles, mechanisms of action, and possible safety issues of LBPs in certain gut-brain axis-related psychiatric conditions are discussed in the light of novel human and animal studies in this article. In this way, it will serve as a guide for future research and nutrition in clinical practice.

Gut-Brain Axis-Related Psychiatric Conditions

Depression

Depression is one of the most prevalent mental illnesses, impacting around 320 million people worldwide [14]. Genetic, neurological, inflammatory, psychological, cognitive, and environmental factors have all been linked to the development of depression [15]. Different treatment methods are used in the treatment of depression, including pharmacological treatments and psychological therapies [16–19]. It is known that the indicated treatments are efficient in decreasing depression symptoms and that the majority of patients respond to treatment [20]. However, depression may reach advanced dimensions in patients who do not respond to treatment or do not prefer current treatments due to stigma [21]. This raises the issue of additional or complementary treatment strategies for depression [22].

It is accepted that the gut microbiota has a role in regulating psychological health in addition to physical health through the gut-brain axis. Recently, it was found that intestinal microbial abundance and diversity in depressed patients vary according to healthy controls. According to reports, the abundance of *Lachnospiraceae*, *Ruminococcaceae*, *Lactobacillus*, *Bifidobacterium*, and *Firmicutes* decreased in depressed patients, although the abundance of *Bacteroidetes*, *Proteobacteria*, and *Actinobacteria* increased [23, 24]. Negative changes in the intestinal microbiota may cause depression in ways such as increased intestinal barrier permeability, stimulation of systemic inflammation, alteration of tryptophan metabolism, impaired release of monoamine neurotransmitters, and changes in brain-derived neurotrophic factor (BDNF) abundance [25, 26].

Alterations in the gut microbiota may cause resistance to antidepressants in major depressive disorder. It has been reported that responders to antidepressants exhibit greater phylogenetic diversity than non-responders [27].

In the gut microbiota of non-responders, the abundance of the phylum *Actinobacteria*, families *Christensenellaceae* and *Eggerthellaceae*, and genera *Adlercreutzia* and *Christensenellaceae* R7 were detected compared to the responders. It is thought that changes in gut microbiota composition, associated metabolites, and metabolic function may be related to the response to antidepressants [28].

The promotion of systemic inflammation by the gut microbiota may impact mental health. Leaky gut is hypothesized to cause increased inflammation as a result of impaired barrier function. When the permeability of the intestinal barrier increases, microbial products such as lipopolysaccharides induce an inflammatory response [29]. Systemic inflammation caused by leaky gut is hypothesized to disrupt brain activity via pro-inflammatory cytokines that pass the

blood–brain barrier, contributing to symptoms of depression by affecting the central nervous system (CNS) functioning such as BDNF and serotonin signaling [25, 30].

Tryptophan, which is not synthesized in the human body, belongs to the class of essential amino acids. For this reason, tryptophan must be taken into the body from food. The main dietary sources of tryptophan are chicken, turkey, tuna fish, milk, cheese, bread, oats, peanuts, and chocolate [31].

The majority of dietary tryptophan is absorbed in the small intestine. A certain amount of tryptophan reaches the large intestine and is degraded by commensal microbes. The gut microbiota is able to metabolize tryptophan precisely. About 4–6% of tryptophan is metabolized by intestinal bacteria to indican, indole acid derivatives, and tryptamine. Tryptamine, which is structurally similar to serotonin, can be produced from tryptophan by decarboxylases of commensal bacteria [32, 33].

In comparison with humanized mice, germ-free mice were reported reduced levels of tryptamine in the gut. This result suggested that the gut microbiota participates in the modulation of intestinal tryptophan decarboxylation [34].

Tryptophan metabolites are also thought to be effective in the gut-brain interaction. Tryptophan can be converted to serotonin under normal conditions. However, under inflammatory conditions, tryptophan is primarily converted to kynurenine [35]. The tryptophan mechanism is given in Fig. 1. Although kynurenines are important in the immunomodulation, neuroprotection, and energy balance of the CNS at physiological levels, they are known to have neurotoxic and neurodegenerative effects [36]. Pro-inflammatory cytokines, bacterial lipopolysaccharides, glucocorticoids, and oxidative stress can activate enzymes in the kynurenine pathway, causing tryptophan to be converted to toxic tryptophan catabolites. Increased kynurenine levels are thought to have a contribution to the progression of major depressive disorder [37]. Possible mechanisms explaining the link between microbiota, the gut-brain axis, and depression are shown in Fig. 2.

It is thought that LBPs may have an effect on depression symptoms through the gut microbiota. Some current human and animal studies on this subject are given in Table 1 and Table 2 in detail [30, 37–43]. Studies have shown that especially *Bifidobacterium bifidum*, *Bifidobacterium longum*, *Lactiplantibacillus plantarum*, and *Lactobacillus helveticus* strains are prominent in patients with depression [30, 37, 39–41]. In addition, although studies mostly reported improvements in depression symptoms in comparison to a control group [37, 38, 40, 41], there are studies that stated that the state of depression did not change according to some psychological tests [30, 39]. Since depression is a multifactorial mental disorder, evaluating changes in the gut microbiota alone may make it difficult to give clearer recommendations for the use of LBPs.

Anxiety

Anxiety is defined as a mental disorder that brings with it excessive fear, anxiety, and related behavioral disorders.

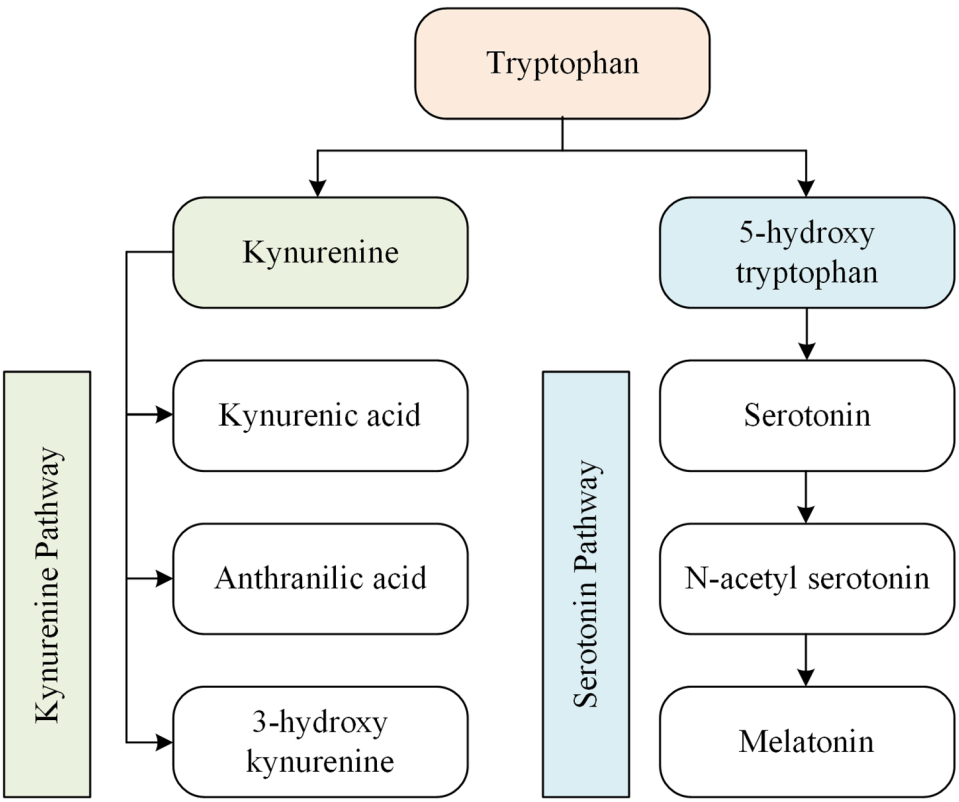

Fig. 1 Biometabolism of tryptophan. Tryptophan is metabolized via kynurenine and serotonin pathways in mammalian cells. In the kynurenine pathway, kynurenine is converted to kynurenic acid, anthranilic acid, and 3-hydroxy kynurenine. In the serotonin pathway, 5-hydroxy tryptophan is produced from tryptophan by tryptophan hydroxylase. 5-hydroxy tryptophan transformed to serotonin, N-acetyl serotonin, and melatonin

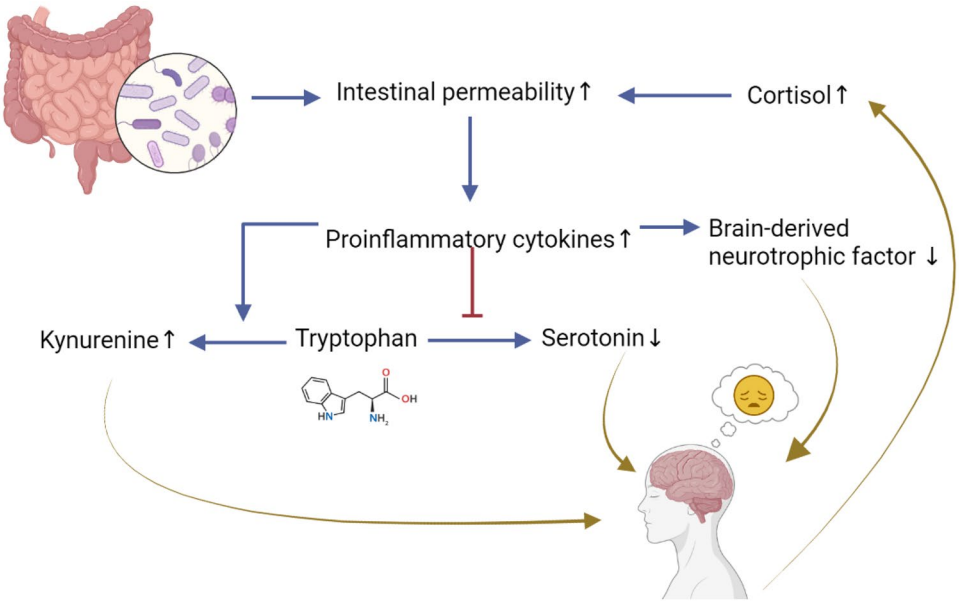

Fig. 2 Relationship between microbiota, gut-brain axis, and depression

This definition includes many conditions such as general anxiety disorder, panic disorder, phobias, and social anxiety [56]. It is estimated that 264 million people in the world have an anxiety disorder [14]. Anxiety disorders are primarily treated with psychological therapy and pharmacotherapy [57].

Dysregulation of the HPA axis causes an increase in the development of mental diseases such as anxiety. It is thought that exposure to stress may exacerbate anxiety [58]. The HPA axis is a component of the stress response. In stressful situations, the HPA axis is activated, and cortisol secretion is increased. Stress-induced dysbiosis of the microbiota may cause dysregulation of the HPA axis by affecting gene expression in the hippocampus and hypothalamus, cortisol levels, and immune system function [59, 60]. It has been reported that the diversity of the gut microbiota is reduced in patients with generalized anxiety disorder compared to healthy individuals [61]. *Faecalibacterium, Butyricicoccus*, *Eubacterium rectale*, *Sutterella*, and *Lachnospira* bacteria are less common in bacteria, while *Bacteroides*, *Escherichia-Shigella*, *Ruminococcus gnavus*, *Lactobacillus*, and *Fusobacterium* are more common in the treatment-naive generalized anxiety disorder patients compared with healthy controls [61]. In another study, a low density of *Firmicutes* and *Tenericutes* bacteria was noted in anxiety patients [62]. It seems possible to talk about a bidirectional relationship between gut microbiota and mental health. It has been reported that changes and interactions originating from the intestinal microbiota, such as vagus nerve-mediated interaction, impaired intestinal permeability, systemic inflammation, and microbial metabolites, may be associated with anxiety, similar to the mechanisms mentioned in depression [63–67].

The vagus nerve provides efferent and afferent transmission, creating a connection between the gut and the brain. Therefore, vagal-mediated effects transmitted to the brain are thought to be influenced by intestinal bacteria. Specific bacterial strains have been shown to use vagus signals to interact with the brain [63]. In a study, it was reported that application of *Campylobacter jejuni* caused anxiety-related behavior in the cell bodies of vagal afferents and the main organ, the nucleus tractus solitarius, and increased c-Fos expression in neurons [64].

It is thought that psychological stress may cause mood disorders such as anxiety through systemic and neural inflammation. Psychological stress can cause an increase in intestinal permeability with the HPA axis and increased cortisol secretion [68, 69]. Increased intestinal permeability activates the immune response by allowing bacterial liposaccharides to enter the bloodstream [70]. Peripheral inflammation can then have negative effects on mental health, such as anxiety, by affecting the CNS, promoting neurotoxins, and inhibiting neurotransmitters [65]. The presence of increased pro-inflammatory cytokine levels and decreased anti-inflammatory responses in individuals clinically diagnosed with anxiety compared to healthy individuals supports the relationship between inflammation and anxiety [71].

Short-chain fatty acids (SCFAs) and tryptophan metabolites are among the key metabolites generated by bacteria in the intestine. Metabolites are considered as signaling molecules that communicate with other microorganisms, the host immune system, or secondary metabolites. It is thought that SCFAs can suppress colonic inflammation and maintain intestinal barrier integrity by increasing tight binding proteins [72]. The interaction of SCFAs induces the secretion of gut hormones and neurotransmitters such as γ-aminobutyric acid (GABA)

Table 1 Novel certain human clinical trials on live biotherapeutic products (LBPs) in gut-brain axis-related conditions

Gut-brain axis-related conditions	LBPs	Subjects	Dose	Intervention duration	Results	Reference
Depression	Sanprobi irritable bowel syndrome (IBS) ® *Lactiplantibacillus Plantarum 299v* (*LP299v*)	Seventy-nine depressed patients *LP299v* ($n=40$) Placebo ($n=39$)	2 capsules/day Each capsule contained (1×10^{10} CFU) colony forming units	8 weeks	• There was an advance in cognitive function in the *LP299v* group • Kynurenine concentration of the *LP299v* group significantly decreased • TNF-α, IL-6, and IL-1 concentrations, in addition to cortisol, did not change significantly in either the probiotic or placebo groups	[37]
Depression	*Bifidobacterium bifidum* BGN4 *Bifidobacterium longum BORI*	Sixty-three healthy elders	Four capsules/per day (1×10^{9} CFU) Placebo (500 mg of soybean oil/capsule)	12 weeks	• In the *Bifidobacterium* group, the relative riches of inflammation-causing bacteria were reduced • Contrary to placebo, serum BDNF levels increased considerably in the *Bifidobacterium* group • Mental flexibility and stress scores improved in the *Bifidobacterium* group • There was no significant difference in depression according to the Korean version of Geriatric Depression Scale	[39]
Depression	*Lactobacillus helveticus* (*R005*) *Bifidobacterium longum* (*R0175*)	Eighty-one depressed patients *Lactobacillus helveticus* and *Bifidobacterium longum* (*n*: 28) Galactooligosaccharide (*n*: 27) Placebo (*n*: 26)	10×10^{9} CFU per 5 g sachet	8 weeks	• *R0052* and *R0175* supplementation reduced Beck Depression Inventory score compared to other groups • Serum kynurenine/tryptophan ratio has not changed between the groups	[40]
Depression	*Lactiplantibacillus plantarum* PS128 (PS128)	Eleven depressed patients	PS128 capsule twice a day 3×10^{10} CFU/each capsule	8 weeks	• The depression scores decreased significantly • Serum levels of inflammatory parameters and the balance of gut microbiota did not approximately change	[41]

Table 1 (continued)

Gut-brain axis-related conditions	LBPs	Subjects	Dose	Intervention duration	Results	Reference
Depression and anxiety	Winclove's ecologic barrier	Three group -Intervention (*n*: 34) -Placebo (*n*: 37) -Healthy (*n*: 20)	Two sachets/day (2.5×10^9 CFU/g)	8 weeks	• All of the individuals improved their symptoms, implying that monitoring visits have non-specific treatment effects • Although probiotics had no effect on the microbiota of depressed people, there was a significant association between *Ruminococcus gnavus* and depression parameter • There was no significant change in the psychological tests	[30]
Depression and anxiety	*Clostridium butyricum* MIYAIRI 588 (*CBM588*)	Forty antidepressant treated inpatients *CBM588* (*n*: 20) Control (*n*: 20)	60 mg/day	8 weeks	• According to the Hamilton Depression Rating Scale-17, Beck Depression Inventory, and Beck Anxiety Inventory scales, *CBM588* in combination with drug caused considerable improvement in depression	[38]
Depression and anxiety	*Bifidobacterium longum*	Seventy-nine undergraduate students *Bifidobacterium longum* (*n*: 40) Placebo (*n*: 39)	Two capsules/day 4×10^{10} CFU *B. longum*/each capsule Placebo 400 mg/capsule cornstarch	1 week	• There was no important difference in anxiety, depression or stress symptoms between groups	[44]
Depression and anxiety	*Lactobacillus acidophilus* W37, *Levilactobacillus brevis* W63, *Lacticaseibacillus casei* W56, *Ligilactobacillus salivarius* W24, *Lactococcus lactis* W19, *Lactococcus lactis* W58, *Bifidobacterium bifidum* W23, *Bifidobacterium lactis* W52	Eighty-three patients with anxiety/depression symptoms	One sachet (2 g of product) 2.5×10^9 CFU per gram	2 months	• The Hospital Anxiety and Depression Scale score improved significantly	[45]

Table 1 (continued)

Gut-brain axis-related conditions	LBPs	Subjects	Dose	Intervention duration	Results	Reference
Anxiety	*Lactobacillus acidophilus*, *Bifidobacterium longum*, *Bifidobacterium bifidum*, *Bifidobacterium lactis*	Forty-eight patients with anxiety disorder (drug-free) Intervention (*n*: 24) Placebo (*n*: 24)	Intervention: one capsule contained 18×10^9 CFU bacteria + 25 mg sertraline Placebo: one capsule contained starch + 25 mg sertraline	8 weeks	• In the intervention group, the Hamilton Rating Scale score (anxiety) decreased • Although the intervention group had a greater reduction in Beck Anxiety Inventory, it was not substantially contrasting from the placebo group • The State-Anxiety Inventory score decreased more in the intervention group	[46]
Anxiety	*Lactobacillus gasseri* CP2305 (CP2305)	Sixty medical students CP2305 (*n*: 29) Placebo (*n*: 31)	Two tablets/day 1×10^{10} bacteria cells per two tablets	24 weeks	• The Spielberger State-Trait Anxiety Inventory and the Pittsburgh Sleep Quality Index both showed that taking the CP2305 tablet reduced anxiety and sleep disturbance • CP2305 treatment reduced the *Bifidobacterium* spp. and the increased *Streptococcus* spp. in feces	[47]
Depression and bipolar disorder	*Lacticaseibacillus paracasei strain Shirota*	Eighteen patients with depression or bipolar disorder	8.0×10^{10} CFU/day	12 weeks	• Hamilton Depression Rating Scale score decreased • The *Actinobacteria* phylum was kept at a greater count	[48]
Bipolar disorder	OMNi-BiOTiC® Stress Repair	Twenty-seven individuals with bipolar disorder	1 portion (= 3 g) 7.5×10^9 CFU	3 months	• Mania scale scores decreased • Depression Scale score unchanged	[49]
Bipolar disorder	*Lacticaseibacillus casei*, *Lactobacilus acidophilus*, *Lacticaseibacillus rhamnosus*, *Lactobacilus bulgarigus*, *Bifidobacterium breve*, *Bifidobacterium longum*, *Streptococcus thermophiles*	Thirty-eight patients with type 1 bipolar disorder Intervention (*n*: 19) Placebo (*n*: 19)	One capsule 1.8×10^{10} CFU/capsule	8 weeks	• Mania and depression scale scores decreased in intervention group, but it was not significant	[50]

Table 1 (continued)

Gut-brain axis-related conditions	LBPs	Subjects	Dose	Intervention duration	Results	Reference
Bipolar disorder	OMNi-BiOTiC® Stress Repair	Twenty euthymic individuals with bipolar disorder	1 portion (= 3 g) 7.5×10^9 CFU	3 months	• The Digit Symbol Test showed that after treatment, performance in terms of attention and psychomotor processing speed improved • Over 3 months, executive improved	[51]
Bipolar disorder	*Lacticaseibacillus rhamnosus strain GG* *Bifidobacterium animalis* subsp. *lactis strain Bb12*	Sixty-six patients hospitalized for mania Intervention (*n*: 33) Placebo (*n*: 33)	One tablet/day $>10^8$ CFU	24 weeks	• Psychiatric hospitalization time decreased in intervention group • Intervention resulted in fewer days rehospitalization • Patients with significant levels of systemic inflammation at baseline had a higher chance of avoiding rehospitalization	[52]
Schizophrenia	*Lacticaseibacillus rhamnosus strain GG* *B. Animalis* subsp. *lactis strain Bb12*	18–65 years Fifty-six patients	10^9 CFU/day	14 weeks	• Supplementation had no significant difference on Positive and Negative Syndrome Scale (PANSS) scores, but positive symptoms have a bigger impact than negative symptoms • Significant reduction in the number of *Candida albicans* antibodies	[53]

Table 1 (continued)

Gut-brain axis-related conditions	LBPs	Subjects	Dose	Intervention duration	Results	Reference
Schizophrenia	*Bifidobacterium breve* A-1	Responders (*n*: 12) Non-responders (*n*: 17)	10^{11} CFU/day	4 weeks intervention 4 weeks observation	• Anxiety/depression score were significantly improved • Responders displayed higher relative abundances of 5 functional genes involved in metabolism, protein processing in the endoplasmic reticulum, and the insulin signaling pathway than non-responders • Responders had increased abundances of useful genes associated to energy and lipid metabolism • The effects of intervention on anxiety and depressed symptoms may be linked to higher lipid and energy metabolism at baseline • In schizophrenia patients, *Bifidobacterium breve* A1 improved anxiety and depressed symptoms	[54]

Table 2 Novel certain animal model studies on live biotherapeutic products (LBPs) in gut-brain axis-related conditions

Gut-brain axis-related conditions	LBPs	Subjects	Dose	Intervention duration	Results	Reference
Depression	*Bifidobacterium longum* subsp. *infantis* E41 *Bifidobacterium breve* M2CF22M7	C57BL/6 J mice 4 group -Healthy control -Control chronic moderate stress -Fluoxetine -Intervention	10^9 CFU/day	5 weeks	• E41 and M2CF22M7, which increased the expression of Tph1 and secretion of 5-hydroxytryptophan • E41 and M2CF22M7 reduced depressed behaviors in mice • The levels of 5-hydroxytryptamine and BDNF increased in the brain • M2CF22M7 reduced the serum cortisol concentration • Chronic-stress-induced microbial dysbiosis was found to be improved by E41 and M2CF22M7	[43]
Depression and anxiety	*Bifidobacterium breve* CCFM1025	Forty male mice (C57BL/6 J) 4 group -Healthy control -Control chronic moderate stress -Fluoxetine -*Bifidobacterium breve* CCFM1025	10^9 CFU/day	5 weeks	• CCFM1025 decreased depression and anxiety-like behaviors • CCFM1025 increased the expression of BDNF • SCFA and 5-HTP levels are increased, and chronic stress-induced intestinal microbial abnormalities are regulated • Intestinal 5-HTP synthesis was favorably linked with stool SCFA and *Bifidobacterium breve*	[42]
Depression and anxiety	Heat killed *Enterococcus faecalis strain* EC-12	Sixteen male C57BL/6 J mice EC-12 group (*n*: 8) Control group (*n*: 8)	AIN-93 M diet with heat-killed EC-12	4 weeks	• In the open-field, the EC-12 group demonstrated lower anxiety-like behavior and a higher plus-maze test score • The forced swim test showed that EC-12 supplementation has an anti-depressive effect • With EC-12, there was a considerable increase in *Butyricoccus* and *Enterococcus* in the gut microbiota	[55]

and serotonin, boosting indirect brain communication via the circulatory system or vagal pathways [66, 73–76]. It also affects glial cell morphology and function in the CNS, modulates neurotrophic factor levels, promotes neurogenesis, and aids serotonin manufacturing, all of which help to manage neuroinflammation [66, 77–79]. Changing intestinal microbiota diversity and the decrease in SCFAs can trigger mood disorders and other mental problems due to their effect on the pathways [66]. Serotonin is an essential neurotransmitter that regulates anxiety and mood, and some medications commonly used to treat anxiety disorders aim to increase serotonin levels in the CNS. Tryptophan is an important precursor for the production of both serotonin and kynurenine, as indicated in Fig. 1 [35]. Tryptophan catabolites formed by the kynurenine pathway from tryptophan are known as important pathophysiological metabolites of anxiety. It is thought that indoleamine-2,3-dioxygenase, which is involved in this pathway, is activated by pro-inflammatory cytokines, and therefore is associated with the psychoimmunological mechanism of anxiety [67]. Improvement of intestinal microbiota and control of inflammation in anxiety patients will contribute to the regulation of kynurenine and tryptophan metabolism, which affect serotonin production.

Short-chain fatty acids also have effects on epigenetics. Metabolites secreted from the gut microbiota can affect histone modifications and DNA methylations [80]. Histone deacetylation and expression decreased as a result of acetate supplementation, which is one of the short-chain fatty acids [81]. Butyrate can also inhibit histone deacetylation and affect DNA methylation [82, 83]. It has been suggested that it may also exert an immunomodulatory effect by inhibiting histone deacetylation [82]. Since anxiety is associated with epigenetic factors, SCFAs may also act through these pathways [84].

It is thought that LBPs may have positive effects on anxiety with the same mechanisms as other mood disorders, by reducing inflammation, increasing the production of beneficial intestinal metabolites, regulating tryptophan mediators, and increasing neurotransmitters and neuropeptides [30, 38, 42, 44–47, 55]. Some recent human and animal studies on this subject are detailed in Table 1 and Table 2 [30, 38, 42, 44–47, 55]. Although studies mostly reported improvements in anxiety symptoms compared to the control group [38, 42, 45–47], there are studies stating that the anxiety state does not change according to some psychological tests [30, 44]. Factors such as differences in study groups, microbiome differences, variety of strains used as interventions, and duration of use may lead to differences in study results.

Bipolar Disorder

Bipolar disorder is a recurrent psychopathological condition characterized by fluctuations in mood [85]. Bipolar disorders include bipolar I, bipolar II, cyclothymic, and other defined bipolar and related disorders, according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-5). It is recommended that the treatment of bipolar disorder be determined according to the current mood characteristics (such as mania, hypomania, or depression) [56]. In bipolar disorders, pharmacological treatments come to the fore in order to prevent the recurrence of mood episodes. It is known that mood stabilizers or antipsychotic drugs such as lithium, valproate, which are very effective on the disease, can cause serious long-term side effects [86, 87]. Situations that may reduce patients' adherence to treatment, such as drug side effects and treatment refusal, focus on the evaluation of alternative therapeutic approaches [88].

Interest in the relationship between the psychological and gastrointestinal systems has expanded significantly due to the search for alternative therapeutic approaches [89, 90]. The increased inflammatory state altered gut microbiota, and low levels of some neurotransmitters detected in patients with bipolar disorder suggest brain-gut interaction [91–97]. Negative factors that are hypothesized to play a function in bipolar disorder's gut microbiome are shown in Fig. 3.

Stress, microglial activation, leaky gut, and some genetic-epigenetic factors are thought to cause inflammation in bipolar disorder [93, 98]. Therefore, it is suggested that at least some of the inflammatory changes seen in the bipolar state possibly linked to the gut microbiome [93]. The composition of the gut microbiota and increased cytokine levels in the inflammatory state come to the fore [96]. Studies have reported decreased abundances of *Faecalibacterium* and *Firmicutes* and increased abundances of *Actinobacteria* and *Coriobacteria* in the gut microbiota of patients with bipolar disorder compared to healthy controls. [92, 95].

Another prominent condition in bipolar disorder is decreased neurotransmitter levels [94]. It is known that *Lactobacillus*, *Bifidobacterium*, *Escherichia*, *Bacillus*, *Streptococcus*, and *Enterococcus* strain are effective on the formation of GABA, norepinephrine, serotonin, dopamine, and acetylcholine, which are neurotransmitters produced by the intestinal microbiota [97]. In addition, tryptophan metabolites, which are mentioned in the depression and anxiety sections, also act as signal molecules. A meta-analysis in bipolar patients shows reduced levels of tryptophan and tryptophan metabolites compared to controls. [91].

It is thought that LBPs may exert positive effects on bipolar disorder by reducing inflammation, improving gut microbiota, and balancing gut neurometabolites. Current studies on this subject are given in detail in Table 1 [48–52].

Schizophrenia

The term schizophrenia refers to a fragmented or disorganized form of thought, emotion, and behavior. According to

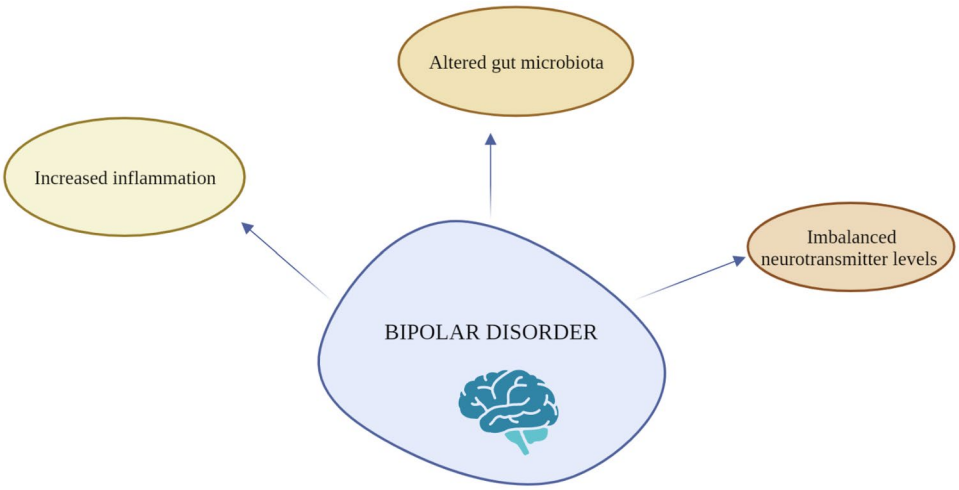

Fig. 3 Some adverse conditions associated with the gut microbiota seen in bipolar disorder

the DSM-5, the diagnostic criteria for schizophrenia consist of three topics as characteristic symptoms, social/occupational dysfunction, and duration (symptoms indicate at least It should have been going on for 6 months). For a diagnosis of schizophrenia, at least one of the first three symptoms delusions, hallucinations, and disorganized speech, must be met [56]. Schizophrenia is a serious neurodevelopmental disorders that affects 20 million individuals annually around the world. [99].

Antipsychotics, psychotherapy and psychobiotics are used in the current treatment of the disease [100]. Antipsychotics cause constipation, so this problem is seen in half of schizophrenic patients and poses a serious threat. Gastritis, enteritis, colitis, and IBS are among the gastrointestinal symptoms common in schizophrenia [101–103].

Although the etiology of schizophrenia is not clear, it consists of a combination of genetic, epigenetic, and environmental factors, including gut microbiota [104–107]. One of the major advances in schizophrenia research has been to identify changes in the composition of the gut microbiota of patients with schizophrenia [108]. Schizophrenia is associated with gut dysbiosis [109]. Evidence from case–control studies has repeatedly demonstrated that patients have lower microbial diversity, with a connection between certain microbial taxa and treatment-resistant characteristics of psychosis [110, 111]. It is stated that there is a significant increase in *Lactobacilli* in schizophrenia. [112, 113]. Preclinical evidence shows that disease-specific drugs increase *Firmicutes* and decrease *Bacteroidetes*, consistent with clinical reports in both sexes [114]. Changes in the microbiota of individuals in the presence of schizophrenia are given in Table 3.

Recent breakthroughs in schizophrenia have demonstrated that the gut microbiota can cause neurodevelopmental and neurodegenerative conditions by communicating with the brain via the gut-brain axis, which includes tryptophan metabolism [118], neurotransmitters, immunomodulatory pathways, and bioactive microbial metabolites [119, 120]. There is also a relationship between antidepressants, and microbiota. Differences were found in the microbiota compositions of patients with schizophrenia who response or resistance to antipsychotic treatment [121, 122]. Similarly, microbiota composition was found to be different in patients with schizophrenia treated with typical and atypical antidepressants [122]. Gut microbiota also influence the response to antipsychotics. Enzymes encoded in the microbiota can affect the absorption, distribution, metabolism and elimination of drugs. Bacterial enzymes can exert an indirect effect on pharmacokinetics by modulating metabolic enzymes such as cytochrome P450s [123]. For example, probiotic and dietary fiber supplementation reduced antipsychotic drug-induced body weight gain [124, 125].

The observation of lower serum tryptophan and higher kynurenic acid levels due to changes in the gut microbiota in schizophrenia patients has documented the relationship between tryptophan metabolism modulation and gut microbiota alteration [115, 126]. The vagus nerve directs communication between the gut microbiota and the CNS via metabolites produced by the immune system or the gut microbiota [127, 128]. Neurotransmitters like GABA, dopamine, serotonin, and norepinephrine are among the most prevalent neuroactive substances produced by the intestinal bacteria. It has been stated in many studies that the change in the gut microbiota, which has been studied in schizophrenia patients, causes hypoactivity of N-methyl-D-aspartate and BNDF receptors [126, 129].

Dysbiosis is linked to increased intestinal barrier permeability and the translocation of bacterial antigens into the circulation, as previously discussed. Immune-mediated schizophrenia develops as a result of microbial translocation, which causes neurological damage and apoptosis. Autoimmunity is induced by LPS, which damages the blood–brain barrier. Infiltration of immune cells into the brain can

Table 3 Potential change in microbiota composition in schizophrenia

Increments	Descendants	Reference
*Actinobacteria (Phylum)—Coriobacterio (Class)***	*Firmicutes (Phylum) -*	[106]
Actinobacteria (Phylum) -	*Clostridia (Class)—Clostridiates (Order)—Ruminococcaceae (Family)—Ruminococcus (Genus) and Faecalibacterium (Genus)*	
Actinobacteria (Class)—Actinomycetales (Order)		
Firmicutes (Phylum)—Bacilli (Class)—Lactobacillates (Order)—Lactobacillaceae (Family)—Lactobacillus (Genus)		
*Bacteroidetes (Phylum) – Prevotellaceae (Family)—Prevotella (Genus)**		
Firmicutes (Phylum)—Clostridia (Class)—Clostridiates (Order)—Lachnospiraceae (Family)	*Proteobacteria (Phylum) – Pasteurellaceae (Family) – Haemophilus (Genus)*	[111]
Firmicutes (Phylum)—Vellonelloceae (Family) – Megasphaera (Genus)	*Firmicutes (Phylum)—Clostridia (Class)—Clostridiates (Order)—Ruminococcaceae (Family)***	
*Firmicutes (Phylum)—Clostridia (Class)- Clostridiates (Order)—Ruminococcaceae (Family) – Ruminococcus (Genus)**		
Proteabacteria (Phylum)—Deltaproteabacteria (Class)	-	[115]
Actinobacteria (Phylum) – Bifidobacreiaceae (Family) – Bifidobacterium (Genus)		
Firmicutes (Phylum) – Enterococaceae (Family) – Enterococcus (Genus)		
Firmicutes (Phylum)—Lachnospiraceae (Family) – Lactobacillus (Genus)		
*Firmicutes (Phylum)—Bacilli (Class)—Lactobacillates (Order)—Lactobacillaceae (Family)**	-	[116]
Fusobacteria (Phylum)	*Firmicutes (Phylum) – Lachnospiraceae (Family) – Biotio, Coprococcus, Roseburia (Genus)*	[117]
Bacteriodates (Phylum) – Prevetollecaeae (Family) – Prevotella (Genus)	*Firmicutes (Phylum) – Streptococcoceae (Family) – Streptococcus (Genus)*	
Firmicutes (Phylum)—Lachnospiraceae (Family) – Lactobacillus (Genus)		
Firmicutes (Phylum)—Vellonelloceae (Family) – Megasphaera (Genus)		

*Positively correlated with symptom severity

**Negatively correlated with symptom severity

produce inflammatory cytokines and reactive oxygen strain, leading to neuroinflammation, thereby causing neurodegenerative and neuroprogressive changes in schizophrenia [130, 131]. SCFA levels are reduced due to dysbiosis. This causes disruption of the blood–brain barrier and intestinal mucosal barrier [129]. Possible mechanisms explaining the relationship between microbiota, the gut-brain axis, and schizophrenia are given in Fig. 4.

It is thought that LBPs may have an effect on the symptoms of schizophrenia through the gut microbiota. Some recent human studies on this subject are given in detail in Table 1. LBPs used in two studies given in tablets to schizophrenia patients are *Lacticaseibacillus rhamnosus strain GG*, *B. Animalis* subsp. *lactis strain Bb12*, and *Bifidobacterium breve A-1*. While the Positive and Negative Syndrome Scale score was positively affected by the use of LBPs in Severance's study [53], there was no significant difference between the groups in Yamamura's study. The detection of the relative abundance of genes related to energy and lipid metabolism in individuals responding to intervention with 4-week LBP in the study of Yamamuro [54] emphasizes the importance of initially evaluating functional genes in the gut microbiota before initiating LBPs therapy for patients with mental disorders. Intervention times and applied methods are different in the studies reviewed. More studies are needed to fully demonstrate efficacy in patients with schizophrenia, identify useful specific strains, and the appropriate dose and duration. Evaluation of neurotransmitters and inflammatory cytokines in addition to psychology and symptom evaluation tests that will evaluate the use of LBPs in schizophrenic patients will contribute to a clearer understanding of metabolism in humans and the effectiveness of the supplement used at the level of evidence.

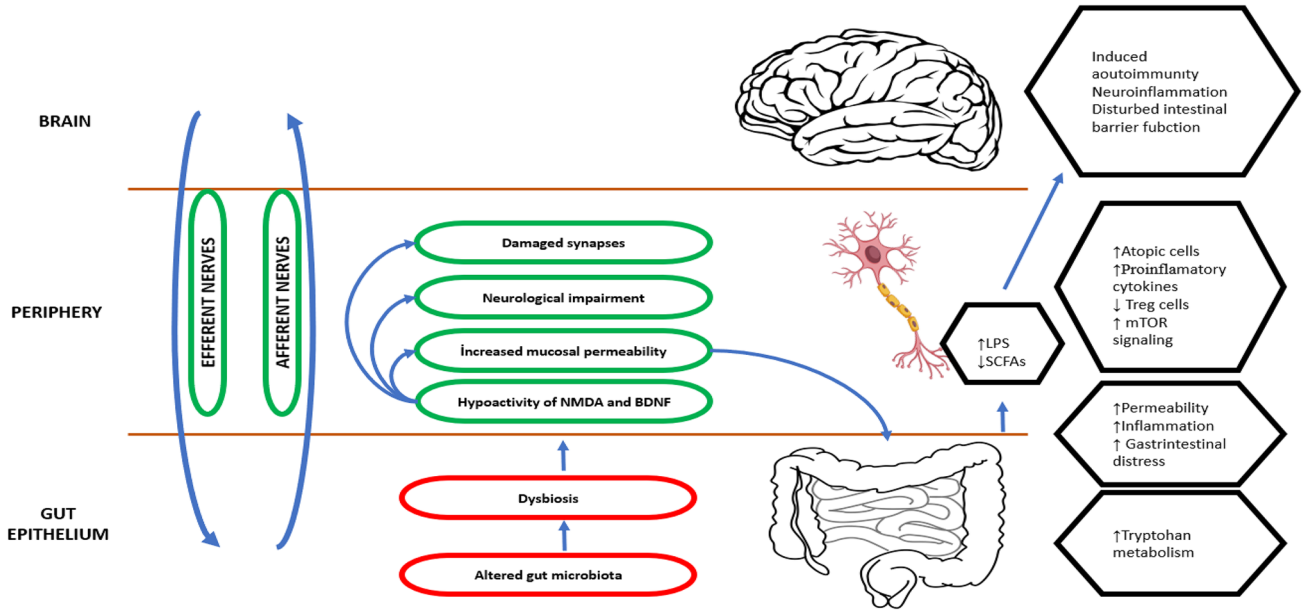

Fig. 4 Relationship between microbiota, gut-brain axis, and schizophrenia (adapted from reference [102])

Conclusion

Recent advances in human and animal research indicate that changes in the gut microbiome and/or metabolites may cause dysbiosis and associated psychiatric conditions. Prevention and treatment strategies for psychological diseases, whose frequencies are increasing day by day, are fundamental issues. Hence, probiotics can be an essential part of nutrition and dietetic practices to prevent and treat these health problems. At this point, one of the most critical prevention and treatment strategies is improving dysbiosis and related harmful metabolites. As a disease-specific therapeutic class, newly emerging LBPs based on probiotics and live bacteria appear promising to prevent and treat potential health problems, including certain psychological conditions, via the gut-brain axis modulation.

Although there is increasing evidence that LBPs have a stabilizing effect on the gut-brain axis and improve certain psychological conditions, it is difficult to establish a standardized nutritional consumption recommendation in line with the novel studies since a variety in the strain, dose, and duration of administration of LBPs applied between studies, and also sample size, not considering the female/male ratio specific to the disease, may cause heterogeneity in the results. Besides, what kind of effect probiotics will have not only in the form of LBPs but also as a component of natural/conventional nutrition, or in other words, on the natural food matrix, is a crucial issue and should be investigated in terms of psychological conditions.

For safety issues, commonly used strains in LBPs such as *Lactobacillus* and *Bifidobacteria* are considered safe. However, the development of the field and the specialization of definitions on this subject necessitate safety and efficacy studies specific to each psychological disease. Thus, guidelines are needed to provide standardization to identify and develop LBPs that could be successful as specific therapeutics for targeted modulation of the gut microbiota-brain axis by authoritarian organizations.

Author Contribution DA designed the study. DA, EÇ, ÖC, FGB, and ÇÖ wrote the main manuscript text. EÇ, ÖC, and FGB prepared all figures and tables. DA, FÖ, and RC critically revised the manuscript. All authors read and approved the final manuscript.

Declarations

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Conflict of Interests The authors declare no competing interests.

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